FORM PTO-1390 (REV 12-29-99) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: CUMP.68854

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/600012

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IB99/00088	01-07-99	01-08-98

TITLE OF INVENTION: METHOD AND APPARATUS FOR MONITORING CEREBRAL PHYSIOLOGY

APPLICANT(S) FOR DO/EO/US: PHILLIPS, Jeffrey Owen; HUCKFELDT, Roger Eugene

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 3 71(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). (unexecuted)
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: Courtesy copy of published application

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U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/600012		

17. ☐ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$970.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$840.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$690.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$670.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$96.00**

	CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	9 - 20 =	0	X **$18.00**	$ 0	
Independent claims	6 - 3 =	3	X **$78.00**	$ 234.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$260.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$ 1,074.00	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$ 537.00	
SUBTOTAL =				$ 537.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 537.00	
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $ 537.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2112. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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REGISTRATION NUMBER: 22,481

METHOD & APPARATUS FOR MONITORING CEREBRAL PHYSIOLOGY

This invention relates to a method and apparatus for monitoring the cerebral cellular environment, especially in patients who have sustained brain injury.

In the event of medical incidents, such as severe trauma to the head, it is frequent practice to monitor the intracranial pressure (ICP) in a ventricle of the brain. An increase in ICP is thought to be indicative of secondary injury such as brain swelling, and it is known to be necessary to relieve pressure by draining cerebrospinal fluid (CSF) if a patient's ICP rises above a critical level. While a body of data exists in the management of intracranial hypertension there have been few investigations of the significance of other cerebral physiological parameters.

The present invention is based on this observation that the pH of CSF is an indicator of the condition of a patient's brain after suffering head trauma and thus the likely outcome of medical treatment.

According to one aspect of the present invention there is provided a method of predicting the outcome of head trauma which comprises monitoring the pH of cerebrospinal fluid (CSF) and comparing the measured pH with a base line representing brain death.

In investigations which have been carried out by the present inventors, a pH sensor was inserted into a cerebral ventricle of a patient and the pH monitored by sequential measurements. Both the rate of change of pH and the absolute level of pH were measured on a continuous basis. While a rapid decrease of pH is a strong indicator of a poor survival prognosis, the absolute value of pH can be used directly to provide a guide to the patients' well being. In general, it has been found that stable levels of pH in the region of 7.15 to 7.25 suggest that the patient is likely to improve clinically, while significantly lower pH levels or continuously falling pH levels are a pointer to poor survival chances. In one case, a pH of about 7.05 correlated with brain stem death.

The present invention also includes apparatus for monitoring the pH and optionally other cerebral physiological parameters which comprises a lumen adapted for introduction through an opening in a skull of a living patient into a cerebral ventricle, said lumen having a pH sensor therein and permitting CSF to flow thereinto and over the sensor.

Preferably, the pH sensor contains a pH-sensitive colour change or fluorescent material and the colour change or fluorescence is measured optically by determining the absorption of a standard light beam.

The catheter containing the pH probe may be a single lumen and may also be used for removing samples of CSF fluid from the ventricle. Alternatively, a bi-lumen catheter may be employed in which the sensor is housed in one lumen and CSF is withdrawn from the other lumen. Removal of CSF may be desirable because of a perceived increase in ICP or may be removed prior to a detected increase in ICP because of a predicted deterioration in the patient's well being because of a fall in pH.

The invention is illustrated by reference to the accompanying drawings in which:-

Figure 1 is a section through a tubular probe containing various sensors;

Figure 2 is a part section through the probe;

Figure 3 is a schematic view showing one way in which the apparatus may be connected to a patient;

Figure 3A is an enlarged view of the Luer lock; and

Figure 3B is a partial section through the patient's head showing one method of introducing the lumen containing the pH sensor.

Referring to the drawings the apparatus comprises a tubular probe (1) comprising a microporous sheath which permits the transfer of CSF into a gel (A) filling the probe. A number of sensors are housed within the tubular probe. One of these is a pH sensor (3). Sensor 3

comprises a length of optical fibre having a mirrored distal end 10 to reflect light back towards the proximal end 11, longitudinally of the optical fibre. Several holes (12) are laser drilled through the optical fibre in a number of random directions normal to the longitudinal axis of the fibre. These holes are filled with a gel containing a phenol red dye which undergoes a colour change with change in pH. A colour change over the pH range from about 6.8 to 7.8 is desirable. The colour shade of the phenol red indicator is determined by passing a light beam along the optical fibre and measuring the absorption spectrum of the reflected beam. After calibration, the absorption spectrum of the reflected beam gives a measure of the pH of the CSF.

As indicated in Figure 1, the tubular probe may also include other sensors such as a CO_2 concentration sensor (pCO_2), 4, a partial oxygen pressure sensor (pO_2), 6, and a thermocouple 5.

Tubular probe 1 is introduced into a ventriculostomy catheter 21 which has a distal end having a foraminous wall to permit CSF to flow into and around the tip of the probe.

The catheter may be introduced into the patient's skull and retained in place with a tubular skull bolt, e.g. as shown in U.S. Patent 4 903 707 (the contents of which are specifically incorporated herein by reference). Conveniently, the catheter is urged into the opening in the

skull as shown schematically in Figure 3 until expression of CSF indicates that the catheter tip has reached the cerebral ventricle.

Referring to Figure 3, the catheter 21 has a distal end into which the tip of the probe is positioned. In the Example illustrated, the catheter comprises a single lumen, e.g. of PVC or polypropylene. The catheter is connected via a Luer lock to an extension tube 13 which may incorporate a side port (not shown) for sampling CSF and monitoring ICP. The extension tube is further connected by optical fibres to a detection, monitoring and display equipment.

Apparatus which is commercially available for intravascular blood monitoring under the registered trade mark 'Paratrend' 7 (Diametrics Medical Ltd 5, Manor Court Yard, Hughendon Ave, High Wycombe, HP13 5RE, United Kingdom) may be adapted for monitoring the pH of CSF by providing means for holding the sensor lumen in place in the skull. This may involve a bolt as described in the above cited US patent 4903707 or secured by other fixing means as indicated in Figure 3B. Referring to this latter Figure it can be seen that the catheter 21 is fixed to the patient's head by securing means 14, passes under the scalp in contact with the skull 15 and then through an opening in the skull and brain 16 to reach a brain ventricle 17. The small, size and flexibility of the catheter (about 2-3 mm diameter) facilitates introduction of the

catheter. The distal tip of the catheter is provided with holes to permit flow of CSF therethrough and around the tip of the probe which is also located within the cerebral ventricle.

Example

16 patients admitted to hospital following brain trauma resulting in severe brain injury (GCS $\leq$ 8) were included in the study. A 'Paratrend 7' sensor measuring pH, pCO_2 and pO_2 was advanced into a ventriculostomy. Sensor data was stored into a computer and transferred to a spreadsheet, pH, pCO_2, pO_2, 1CP, CPP, patent manipulation and outcome were monitored.

Six patients were excluded due to technical difficulties in obtaining and recording data early in the study.

Four patients were found to have initial pH in the range 7.15 to 7.22 but had progressive CSF acidemia over the next 24 to 48 hours. All progressed to herniation and brain death. Clinical evidence of brain death occurred as the pH approached 7.05.

Two patients were found to have a relative high initial CSF pH in the range 7.20-7.25. These values remained substantially constant and both patients remained vegetative.

In the remaining four patients initial pH was in the range 7.12 to 7.24 but increased over the following 48 hours. All displayed significant clinical recovery.

It was found that patient care activities and other known stressors were found to cause a rapid decrease in CSF pH which resolved shortly after the activity stopped. All negative changes in brain pH occurred significantly before elevations of ICP or change in CPP could be detected. This suggests that CSF pH is a more effective indicator of a patient's neurological condition since remedial action can be taken earlier. It was also noted that measurement of CSF pH provides a means for monitoring cerebral ischemia following blunt head trauma. Falling pH correlates to ongoing cellular injury and occurs well before increases in intracranial pressures.

CLAIMS:-

1. A method of predicting the outcome of head trauma comprising monitoring the pH of cerebrospinal fluid (CSF) with time within the initial 24 hours following trauma.

2. A method of claim 1 wherein a change of CSF pH is monitored within the initial 48 hours following trauma.

3. A method of claim 1 wherein the pH of CSF is monitored with a pH probe received in a ventricle of the patient.

4. A method of claim 1 wherein the measured pH is compared with a base line correlating with brain death.

5. A method of treating head trauma, comprising the steps of:

i. monitoring the change of cerebrospinal fluid pH with time within the initial 24 hours following trauma; and

ii. managing the patient such that the pH rises with time.

6. Apparatus for predicting the outcome of head trauma, the apparatus comprising:

a) a pH probe for reception in a patient's brain ventricle and capable of monitoring the pH of CSF;

b) means for calculating the pH at the probe at sequential times;

c) means for comparing the calculated pH values with stored values; and

d) means for displaying and/or recording the resulting values.

7. The use of the measured changes of CSF pH with time in diagnosis or therapy of neurological injuries.

8. The use of means for monitoring the change of CSF pH over time in the manufacture of apparatus for diagnosing the outcome of blunt head trauma.

9. The use of means for monitoring the change of CSF pH with time in the manufacture of apparatus for the therapy of blunt head trauma.

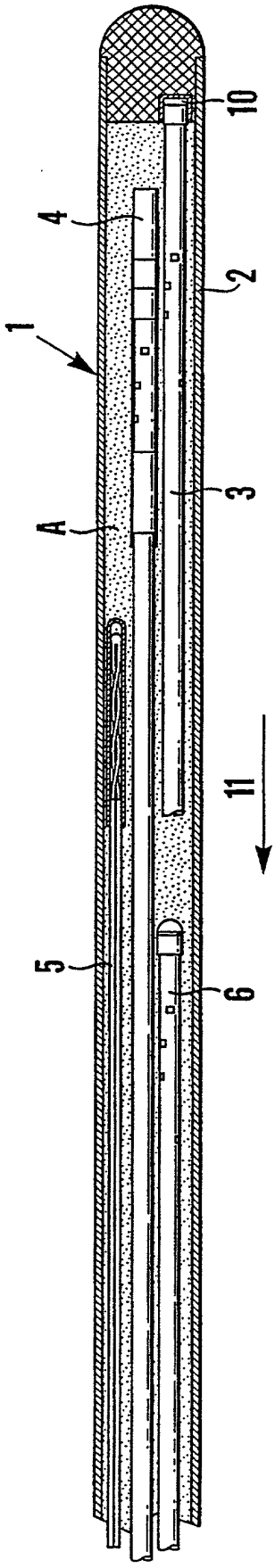

Fig. 1

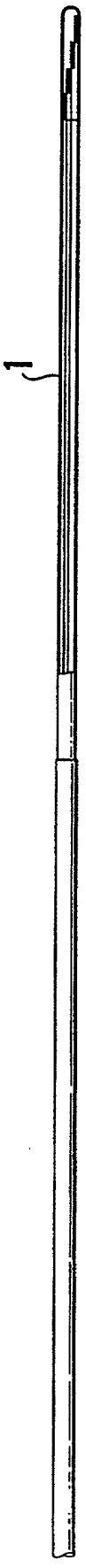

Fig. 2

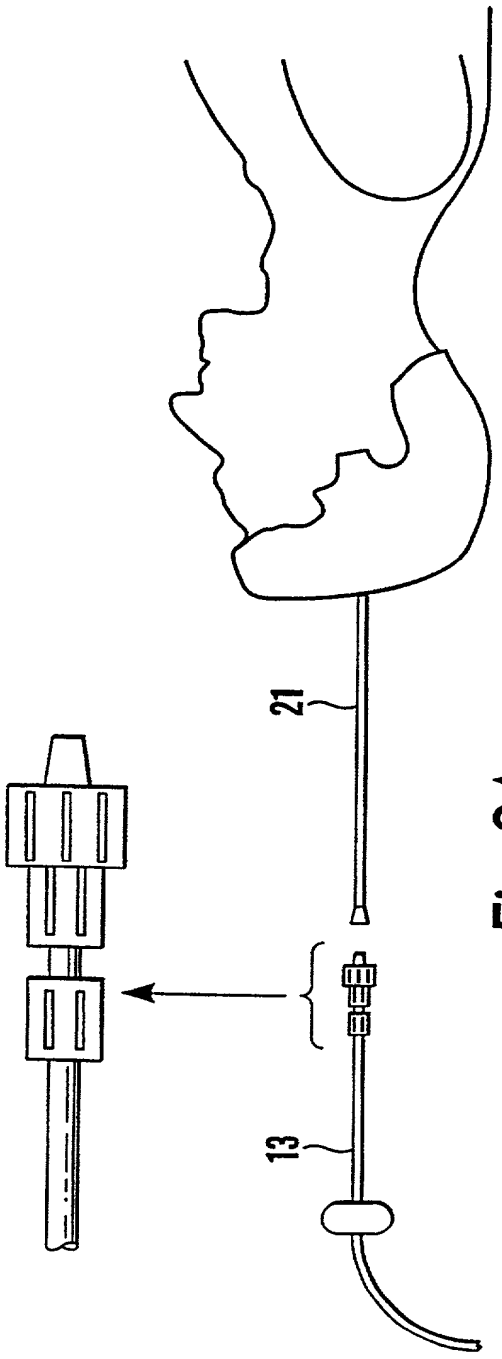

Fig.3A

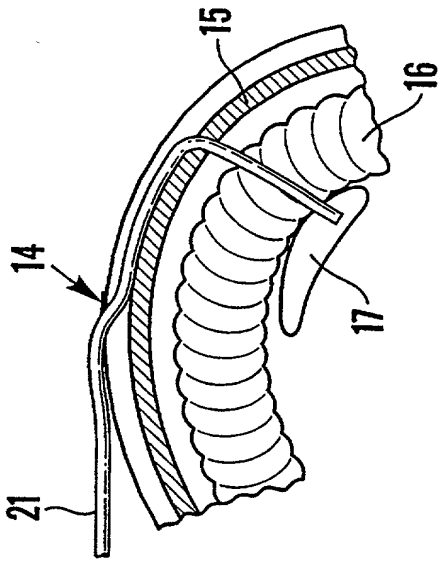

Fig.3B

JOINT DECLARATION FOR PATENT APPLICATION

As below-named inventors, we hereby declare that:

Our residence, post office address and citizenship are as stated below next to our respective names.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled **METHOD AND APPARATUS FOR MONITORING CEREBRAL PHYSIOLOGY**, the specification of which is attached hereto.

We hereby state that we have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, 1.56(a).

We hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed: GB Serial No. 9800370.0; filed 01-08-98; and International Application No. PCT/IB99/00088; filed 01-07-99.

We hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application: NONE.

We hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and to file and prosecute any corresponding foreign applications, including any international applications under the Patent Cooperation Treaty or the European Patent Convention: William B. Kircher, Reg. No. 22,481; James H. Marsh, Jr., Reg. No. 24,533; J. David Wharton, Reg. No. 25,717; Joseph B. Bowman, Reg. No. 25,807; Richard R. Johnson, Reg. No. 27,452; Walter R. Brookhart, Reg. No. 29,518; James H. Riley, II, Reg. No. 31,131; Joan Optican Herman, Reg. No. 31,968; Michael B. Hurd, Reg. No. 32,241; Devon A. Rolf, Reg. No. 35,337; Michael J. Gross, Reg. No. 35,528; William P. Jensen, Reg. No. 36,833; Daniel W. Shinn, Reg. No. 40,810; B. Trent Webb, Reg. No. 40,865; Susan J. Wharton, Reg. No. 41,524; Scott B. Strohm, Reg. No. 42,172; and Clinton G. Newton, Reg. No. 42,930. Address all correspondence to William B. Kircher, SHOOK, HARDY & BACON L.L.P., One Kansas City Place, 1200 Main Street, Kansas City, Missouri 64105-2118, telephone number (816) 474-6550.

We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

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2-00

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